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Palladium(II)-Catalyzed C–H Bond Activation/C–C and C–O Bond Formation Reaction Cascade: Direct Synthesis of Coumestans

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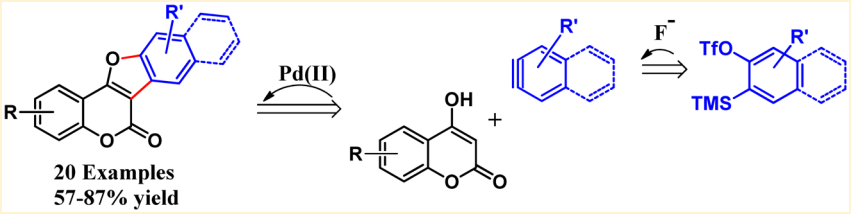
Supporting Information



ABSTRACT: A palladium catalyzed cascade reaction of 4-hydroxycoumarins and *in situ* generated arynes has been developed for the direct synthesis of coumestans. This cascade strategy proceeds via C–H bond activation/C–O and C–C bond formations in a single reaction vessel. This methodology affords moderate to good yields of coumestans and is tolerant of a variety of functional groups including halide. The methodology was applied to the synthesis of natural product flemichapparin C.

Coumestan constitutes the central core unit of a variety of natural polycyclic lactones[1] with important biological activities[2] including anticancer, antibacterial, antifungal, antimyotoxic, and phytoalexine effects. Most importantly, they are known as nonsteroidal "dietary estrogens". Some of the coumestans have the same binding affinity for the ER-β estrogen receptor as 17β-estradiol.[3] Figure 1 shows some of the

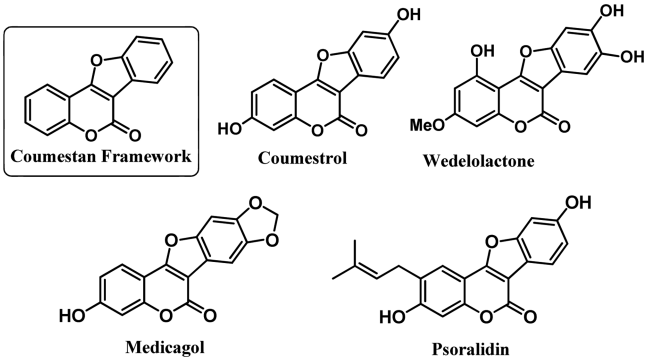


Figure 1. Examples of some naturally occurring coumestans.

naturally occurring biologically active coumestans such as coumestrol, wedelolactone, medicagol, and psoralidin. A wide range of biological properties make coumestans an interesting synthetic target for chemists.

The total syntheses of coumestans particularly coumestrol, wedelolactone, psoralidin, and flemichapparin have been reported by several groups using quite different approaches with modest overall yields.[1d,4] Because of impressive biological activities, particularly estrogenic, it is highly desirable to develop more efficient and general synthetic methods for the synthesis of coumestans and their derivatives. In this regard, a number of synthetic methods have been developed for the construction of this privileged structural unit. For example, syntheses of coumestan derivatives have utilized Pd-catalyzed C–S activation followed by intramolecular transesterification of 2-(methylthio)benzofuran-3-carboxylates and 2-hydroxyphenylboronic acid,[5a] iodocyclization and Pd-catalyzed intramolecular lactonization of acetoxy-containing 2-(1-alkynyl)anisoles,[5b] base-catalyzed condensation of phenyl acetic acid methyl ester with benzoyl chloride followed by intramolecular cyclization,[5c] LDA-induced migration of heterobiaryl *O*-carbamates,[5d] Ag_2CO_3/Celite mediated construction of a furan ring from 1,3-dicarbonyl compounds and vinyl sulfides followed by dehydrogenation,[5e] and aerobic iron-based cross-dehydrogenative coupling of β-ketoesters and phenols.[5f] In addition to these, derivatives of 4-hydroxycoumarins have also been extensively used to lead to diversified coumestan derivatives. In this regard, $FeCl_3$-mediated intramolecular oxidative annulation of 4-hydroxy-3-phenyl-2*H*-chromen-2-one derivatives,[6a] Pd-catalyzed intramolecular arylation of 4-(aryloxy)-3-halocoumarins,[6b] double C–H activations of 4-phenoxy-2-coumarins,[6c] and intramolecular C–H bond functionalization[6d,e] are notable examples (Figure 2). However, in all the cases, prefunctionalizations of 4-hydroxycoumarins are required to obtain the starting materials. Detsi et al. reported the use of enzyme peroxidase from onion solid waste for the synthesis of coumestans from catechols and 4-hydroxycoumarins in satisfactory yields.[7] While there are presently a number of useful synthetic procedures to prepare these compounds, there

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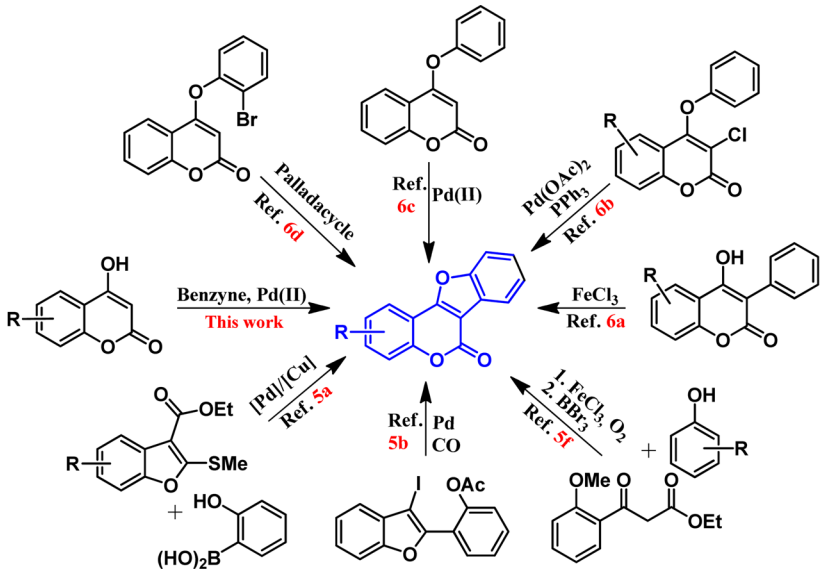
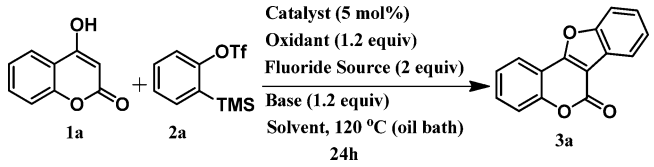


Figure 2. Some synthetic approaches to coumestans.

Table 1. Optimization Studies[a]



entry	catalyst	oxidant	fluoride source	base	solvent	isolated yield **3a** (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	CsF	K_2CO_3	CH_3CN	47
2	$Pd(OAc)_2$	air	CsF	K_2CO_3	CH_3CN	trace
3	$Pd(OAc)_2$	$Cu(OAc)_2$	CsF	–	CH_3CN	trace
4	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**CsF**	**NaOAc**	**CH_3CN**	**81**
5	–	$Cu(OAc)_2$	CsF	NaOAc	CH_3CN	ND
6	$Pd(PPh_3)_4$	$Cu(OAc)_2$	CsF	NaOAc	CH_3CN	59
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	CsF	NaOAc	CH_3CN	39
8	$[RuCl_2(p\text{-Cymene})]_2$	$Cu(OAc)_2$	CsF	NaOAc	CH_3CN	47
9	$Pd(OAc)_2$	$K_2S_2O_8$	CsF	NaOAc	CH_3CN	15
10	$Pd(OAc)_2$	Ag_2O	CsF	NaOAc	CH_3CN	39
11	$Pd(OAc)_2$	$Cu(OAc)_2$	CsF	NaOAc	DMSO	61
12	$Pd(OAc)_2$	$Cu(OAc)_2$	CsF	NaOAc	DMF	59
13	$Pd(OAc)_2$	$Cu(OAc)_2$	CsF	NaOAc	dioxane	60
14	$Pd(OAc)_2$	$Cu(OAc)_2$	TBAF	NaOAc	CH_3CN	39
15	$Pd(OAc)_2$	$Cu(OAc)_2$	KF	NaOAc	CH_3CN	22
16	–	–	CsF	–	CH_3CN	ND

[a]Conditions: 4-Hydroxycoumarin (1.0 mmol), *o*-Silyl aryl triflate (1.5 mmol), catalyst (5 mol %), oxidant (1.2 mmol); fluoride source (2 mmol); base (1.2 mmol), CH_3CN (5 mL) stirred in Ace pressure tube at 120 °C. [b]Isolated yield. ND: Not detected.

remain several limitations as well. (i) Most of the reported procedures involve multiple steps with moderate overall yield. (ii) The starting materials are often not very readily available. (iii) Harsh reaction conditions are usually required. In view of these limitations, the development of an efficient strategy for the synthesis of coumestan is highly desirable.

Arynes have been successfully used for the development of several useful synthetic methodologies[8] and demonstrated as a versatile intermediate for the synthesis of natural products.[9] There are several methods for the generation of arynes;[10] however, Kobayashi's protocol[10a] using *o*-silyl aryl triflate and a fluoride source provides an excellent opportunity to demonstrate the application of arynes in various useful synthetic methodologies. In addition, palladium-catalyzed C−H activation/C−C bond formation has emerged as a powerful tool for chemical synthesis.[11] This synthetic strategy is attractive from the viewpoint of synthetic simplicity and step economy. Recently, Xu[12] et al. reported a palladium-catalyzed oxidative annulation of acrylamides with benzyne precursors for the synthesis of quinolinones via a N−H activation/Heck reaction strategy. Much progress has been achieved in terms of synthesis efficiency and atom economy in the highly selective functionalization of C−H bonds involving directing substituents. In this regard, we envisaged here the Pd-catalyzed C−H activation of 4-hydroxycoumarins followed by C−C and C−O bond formations with reactive intermediate arynes to access

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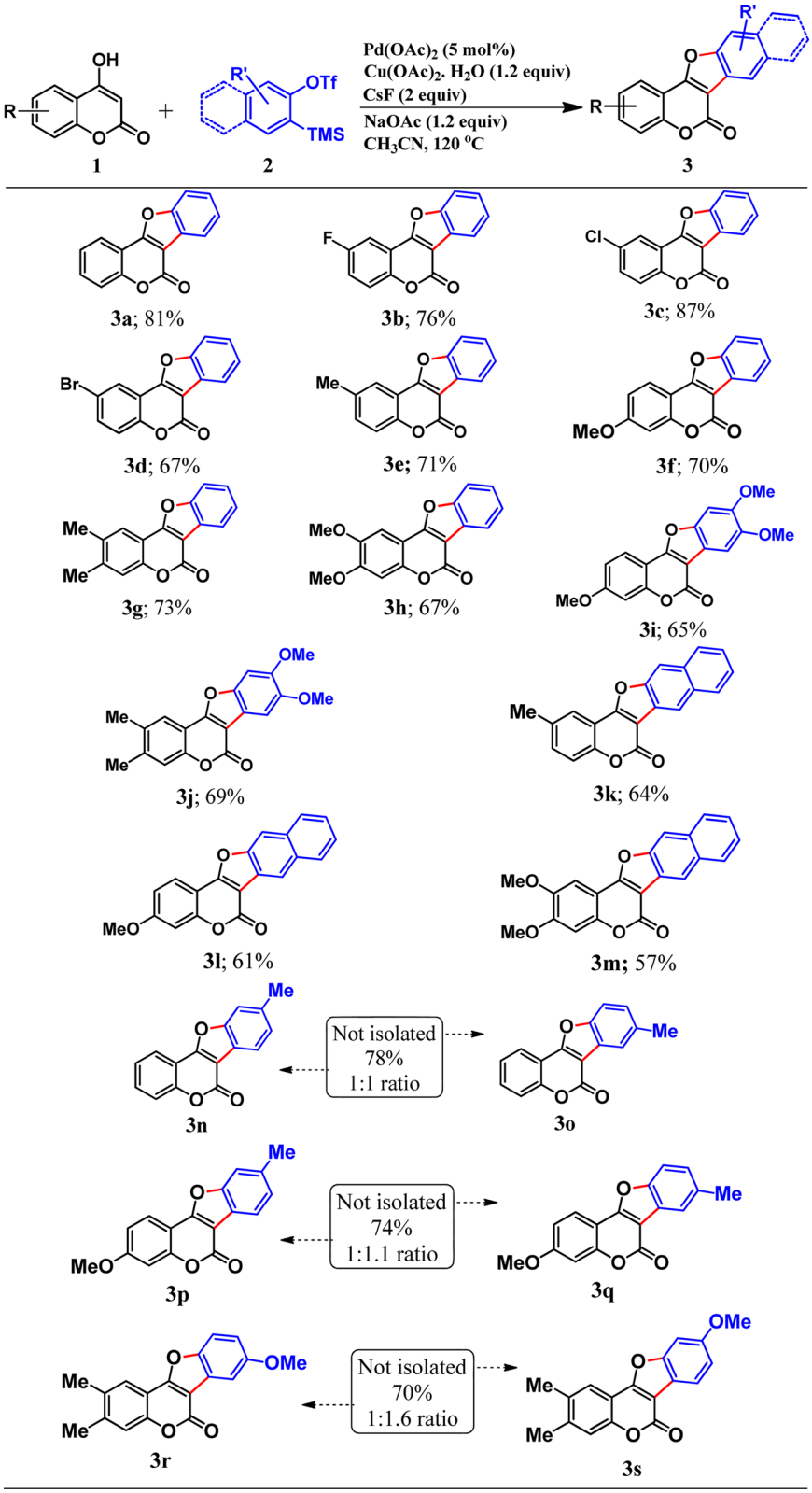
Table 2. Cascade Synthesis of Coumestans from 4-Hydroxycoumarins and Benzyne Precursors[a]



[a]Conditions: 4-Hydroxycoumarin (1.0 mmol), *o*-silyl aryl triflate (1.5 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.2 mmol); CsF (2 mmol); NaOAc (1.2 mmol), CH_3CN (5 mL) stirred in Ace pressure tube at 120 °C for 24 h.

synthetically useful and biologically important coumestan derivatives.

To achieve this challenging transformation, we optimized our reaction conditions employing 4-hydroxycoumarin **1a** and benzyne precursor **2a** as model substrates (Table 1). After a detailed investigation, the oxidative annulation of **1a** with **2a** gave coumestan **3a** in 81% yield under the optimized conditions (Table 1, entry 4).

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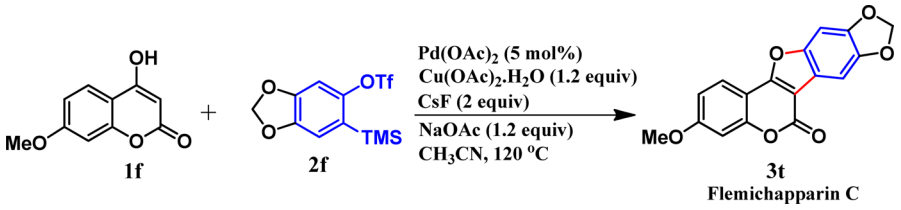
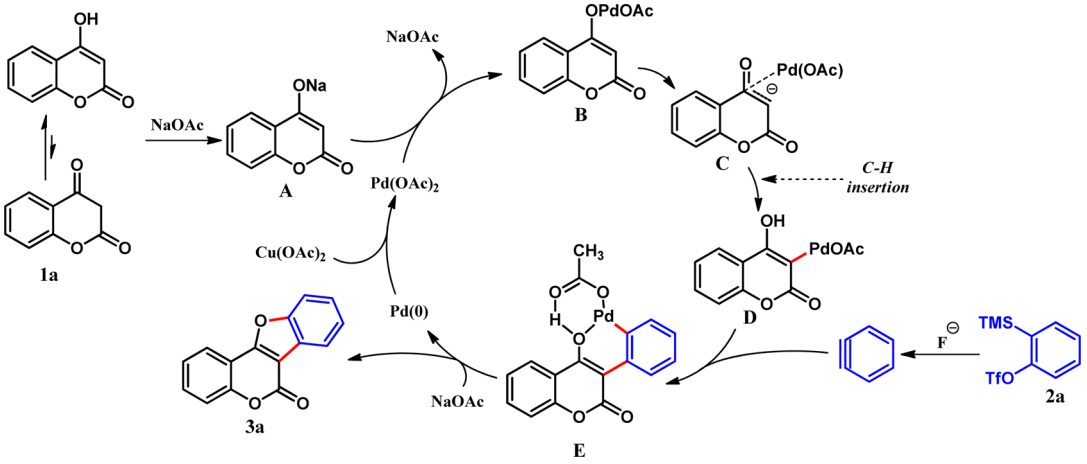
Scheme 1. Synthesis of Flemichapparin C



Scheme 2. Proposed Mechanism for the Synthesis of Coumestan



The structure of **3a** was confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS analysis and finally compared with the reported data.[13] The choice of Pd(II) catalyst was crucial for our strategy, as when it was replaced with Pd(0) or Rh(III) or Ru(II) catalyst, the desired product was obtained with a low yield (Table 1; entries 6−8). In our optimization studies, various oxidants such as air, Cu(II), $K_2S_2O_8$, and Ag_2O were screened, where air did not work in our catalytic process. On the other hand, $K_2S_2O_8$ and Ag_2O gave only 15% and 39% of **3a** respectively (entries 9 and 10; Table 1). As a control experiment, the reaction was performed in the absence of the catalyst and oxidant, and no desired product **3a** was observed (Table 1, entry 16).

After having the optimized reaction conditions in our hand, we next generalized the Pd(II)-catalyzed C−H bond activation/C−C and C−O bond formation reaction cascade for the synthesis of our targeted coumestans. This cascade oxidative annulation of benzynes with a range of 4-hydroxycoumarins for the one-pot synthesis of coumestans are demonstrated in Table 2. As shown in Table 2, *o*-silyl aryl triflates reacted with a variety of 4-hydroxycoumarins bearing fluoro, chloro, bromo, methyl, methoxy substituents, leading to our desired coumestans in good yields (Table 2; **3a**−**3h**). Most interestingly, coupling-prone functional groups such as chloro and bromo remain intact during our Pd-catalyzed cascade process, which could be used for further functionalization of our synthesized coumestans (Table 2; **3c** and **3d**). Electron-withdrawing groups on 4-hydroxycoumarins gave high yields of coumestans in comparison to neutral or electron-donating groups substituted on 4-hydroxycoumarins in our cascade reaction. A silyl triflate having symmetrical substituents, i.e. 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2b**, participated in our cascade process with 6- and 7-substituted 4-hydroxycoumarins providing targeted coumestans with excellent regioselectivity (Table 2; **3i** and **3j**). 3-(Trimethylsilyl)-2-naphthyl trifluoromethanesulfonate, **2c**, also participated in our cascade for the synthesis of some structurally novel coumestan derivatives (Table 2; **3k**, **3l**, **3m**). However, the extended π conjugation of naphthalyne silyl triflate afforded relatively lower yields of coumestans. Additionally, monosubstituted silyl triflates, i.e. 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2d** and 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2e**, were also used as aryne precursors for our reaction. Benzyne from silyl triflate **2d** fused with 4-hydroxycoumarin and 7-methoxy-4-hydroxycoumarin provided coumestans **3n**/**3o** and **3p**/**3q** as regioisomers with 1:1 and 1:1.6 ratios, respectively. On the other hand, when 6,7-dimethoxy-4-hydroxycoumarin is treated with **2e**, the coumestans **3r** and **3s** were formed as regioisomers with a 1:1.6 ratio. The regioisomers are not separated, and their ratios are calculated from ^{1}H NMR.

In order to explore the synthetic application of our Pd(II)-catalyzed cascade strategy, effort was focused toward accessing the coumestan group of natural product flemichapparin C. Commercially available 4-hydroxy-7-methoxycoumarin **1f** was coupled with benzyne precursor 5-(trimethylsilyl)benzo[*d*]-[1,3]dioxol-6-yl trifluoromethanesulfonate **2f** under the optimized reaction conditions. The product flemichapparin C **3t** was formed in 67% yield with excellent regioselectivity (Scheme 1). The requisite aryne precursor **2f** was efficiently synthesized from sesamol according to the known literature procedure.[14] Notably, the present cascade strategy proves a single-step route to this natural product, in comparison to long and complex chemical[6b,c,15] or enzyme-mediated routes.[16]

At present, the exact mechanism of Pd(II)-catalyzed method for the synthesis of coumestans is not clear; however, a plausible reaction mechanism for this reaction is shown in Scheme 2 based on our experiments and reported mechanisms.[17] We assume that the sodium salt of 4-hydroxycoumarin

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and palladium(II)acetate exchanges their alkoxide anions to form the Pd-salt of 4-hydroxycoumarin **B**, which then form the anion species **C**. Concurrently, the C3−Pd species **D** is formed via the C−H activation at the 3-position carbon of **C**, which further undergoes carbopalladation[18] of the aryne generated *in situ* from the aryne precursor giving species **E**. Finally, in the presence of a base the intermediate **E** converted to our desired product **3a** and Pd(0), which is reoxidized to Pd(II) by $Cu(OAc)_2$ to complete the catalytic cycle.

In conclusion, we have developed a novel Pd-catalyzed aryne annulation by 4-hydroxycoumarins, which affords moderate to good yields of coumestans. This strategy involves C−H activation as well as C−C and C−O bond formation successively in a single reaction vessel. Additionally this method has advantages over the reported methods, as it does not require prefunctionalization of 4-hydroxycoumarin to have the targeted coumestans. Most interestingly, coupling-prone functional groups such as chloro and bromo remain intact during our cascade process.

EXPERIMENTAL SECTION

General Information. All reactions involving oxygen- or moisture-sensitive compounds were carried out under an argon atmosphere using oven-dried or flame-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Flash column chromatography was performed with silica gel 60 (100−200 mesh). HRMS data were recorded by electronspray ionization with a Q-TOF mass analyzer.

Caution: When heating a sealed tube, do not fill the reaction vessel beyond half volume. High pressures and temperatures are generated which have led to explosions. Thus, all reactions must be run in a fume hood with appropriate blast shielding in place. Pressure Ace pressure tubes were purchased from SIGMA-Aldrich (catalog no. Z181064-1EA).

General Procedure for the Synthesis of Coumestans. An oven-dried Ace pressure tube (15 mL capacity) equipped with a magnetic stir bar was evacuated and filled with argon. 4-Hydroxycoumarine (0.162g, 1 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.364 mL, 1.5 mmol), $Pd(OAc)_2$ (0.011 g, 5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.240 g, 1.2 mmol), NaOAc (0.098g, 1.2 mmol), CsF (0.304 g, 2 mmol), and acetonitrile (5 mL) were added successively at room temperature. The reaction tube again filled with argon and closed with an O-ring and PTFE plug by hand tightening. The reaction mixture was heated at 120 °C (preheated oil-bath) with stirring for 24 h and then allowed to cool to room temperature. Water (10 mL) was added to the reaction mixture, and the organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed, and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (10%) as eluent.

*6H-Benzofuro[3,2-c]chromen-6-one (**3a**).*[13] Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3a** (0.192 g, 81% yield) as a white solid, R_f = 0.6 (10% ethyl acetate/hexanes), mp 180 °C (lit.[13] mp 181−182 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (dd, J_1 = 2.4 Hz, J_2 = 6.6 Hz, 1H), 8.05 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.68 (dd, J_1 = 1.7 Hz, J_2 = 6.9 Hz, 1H), 7.60−7.64 (m, 1H), 7.41−7.52 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 158.1, 155.6, 153.7, 131.9, 126.8, 125.2, 124.7, 123.5, 121.9, 117.5, 112.7, 111.8, 105.9 (one peak is missing due to overlap); IR ($CHCl_3$): 2918, 2849, 1736, 1628, 1498, 1452, 1371, 1320, 1192, 1096, 1083, 1032, 972, 912, 889, 780, 744 cm^{-1}; HRMS (+ESI) Calcd for $C_{15}H_9O_3$ [M + H]$^+$: 237.0552; found: 237.0557.

*2-Fluoro-6H-benzofuro[3,2-c]chromen-6-one (**3b**).* Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3b** (0.193 g, 76% yield) as light yellow solid; R_f = 0.59 (10% ethyl acetate/hexanes), mp 198−201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.4 Hz, 1H), 7.62−7.74 (m, 2H), 7.45−7.55 (m, 3H), 7.29−7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (d, *J* = 2.8 Hz), 158.9 (d, *J* = 245.7 Hz), 157.6, 155.7, 149.8 (d, *J* = 1.6 Hz), 127.2, 126.4, 123.2, 122.0, 119.4 (d, *J* = 34.7 Hz), 119.3, 113.4 (d, *J* = 9.8 Hz), 111.8, 107.4 (d, *J* = 25.8 Hz), 106.6; IR ($CHCl_3$): 2920, 2850, 1763, 1734, 1567, 1451, 1401, 1257, 1157, 1094, 1066, 996, 861, 821, 774, 748, 667 cm^{-1}; HRMS (+ESI) Calcd for $C_{15}H_8FO_3$ [M + H]$^+$: 255.0457; found: 255.0455.

*2-Chloro-6H-benzofuro[3,2-c]chromen-6-one (**3c**).*[5e] Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3c** (0.235 g, 87% yield) as light yellow solid; R_f = 0.59 (10% ethyl acetate/hexanes), mp 219 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (dd, J_1 = 1.2 Hz, J_2 = 7.9 Hz, 1H), 8.01 (d, *J* = 2.5 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, J_1 = 2.5 Hz, J_2 = 8.9 Hz, 1H), 7.47−7.52 (m, 2H), 7.45 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 157.4, 155.6, 151.8, 131.8, 130.2, 127.1, 125.4, 123.1, 121.9, 121.2, 118.8, 113.6, 111.8, 106.5; IR ($CHCl_3$): 2919, 2850, 1760, 1732, 1556, 1447, 1416, 1162, 1094, 1068, 981, 870, 822, 774, 750, 662 cm^{-1}; HRMS (+ESI) Calcd for $C_{15}H_8ClO_3$ [M + H]$^+$: 271.0162; found: 271.0166

*2-Bromo-6H-benzofuro[3,2-c]chromen-6-one (**3d**).* Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3d** (0.211 g, 67% yield) as white solid; R_f = 0.53 (10% ethyl acetate/hexanes), mp 215−217 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 2.3 Hz, 1H), 8.13−8.16 (m, 1H), 7.67−7.71 (m, 2H), 7.46−7.55 (m, 2H), 7.40 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 157.3, 155.6, 152.3, 134.6, 127.2, 125.4, 124.3, 123.1, 121.9, 119.1, 117.4, 114.1, 111.8, 106.5; IR ($CHCl_3$): 2921, 2851, 1757, 1734, 1447, 1162, 979, 872, 820, 775, 750, 665 cm^{-1}; HRMS (+ESI) Calcd for $C_{15}H_8BrO_3$ [M + H]$^+$: 314.9657; found: 314.9651.

*2-Methyl-6H-benzofuro[3,2-c]chromen-6-one (**3e**).* Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3e** (0.177 g, 71% yield) as white solid; R_f = 0.58 (10% ethyl acetate/hexanes), mp 151−153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.18 (m, 1H), 7.80 (br s, 1H), 7.59−7.70 (m, 1H), 7.32−7.51 (m, 4H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 158.2, 155.5, 151.9, 134.5, 133.0, 126.6, 125.1, 123.5, 121.8, 121.5, 117.2, 112.3, 111.7, 105.8, 20.9; IR ($CHCl_3$): 2920, 2850, 1713, 1635, 1570, 1447, 1358, 1320, 1161, 1097, 1077, 1009, 982, 817, 776, 748, 737, 669, 656 cm^{-1}; HRMS (+ESI) Calcd for $C_{16}H_{11}O_3$ [M + H]$^+$: 251.0708; found: 251.0706

*3-Methoxy-6H-benzofuro[3,2-c]chromen-6-one (**3f**).*[6a] Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3f** (0.186 g, 70% yield) as a light yellow solid, R_f = 0.6 (20% ethyl acetate/hexanes, mp 188 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04−8.14 (m, 1H), 7.91 (dd, J_1= 1.9 H_Z, J_2 = 7.3 H_Z, 1H), 7.57−7.67 (m, 1H), 7.39−7.47 (m, 2H), 6.94−7.02 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0, 160.6, 158.3, 155.5, 155.2, 126.0, 125.0, 123.5, 122.8, 121.4, 113.0, 111.4, 105.8, 103.3, 101.3, 55.7; IR ($CHCl_3$): 2921, 2851, 1729, 1613, 1600, 1447, 1427, 1367, 1275, 1254, 1095, 1023, 986, 945, 855, 774, 753, 746 cm^{-1}; HRMS (+ESI) calcd for $C_{16}H_{11}O_4$ [M + H]$^+$: 267.0657; found: 267.0652.

*2,3-Dimethyl-6H-benzofuro[3,2-c]chromen-6-one (**3g**).*[5e] Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3g** (0.193 g, 73% yield) as a light yellow solid, R_f = 0.58 (10% ethyl acetate/hexanes), mp: 208−210 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03−8.14 (m, 1H), 7.67 (s, 1H), 7.56−7.64 (m, 1H), 7.36−7.50 (m, 2H), 7.21 (s, 1H), 2.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 158.3, 155.2, 152.1, 142.1, 133.5, 126.2, 124.9, 123.6, 121.6, 121.5, 117.8, 111.5, 109.9, 104.8, 20.4, 19.2; IR ($CHCl_3$): 2917, 2849, 1741, 1638, 1448, 1375, 1177, 1095, 1055, 866, 776, 749, 737 cm^{-1}; HRMS (+ESI) Calcd for $C_{17}H_{13}O_3$ [M + H]$^+$: 265.0865; found: 265.0863.

*2,3-Dimethoxy-6H-benzofuro[3,2-c]chromen-6-one (**3h**).* Flash column chromatography on silica gel (25% ethyl acetate/hexanes) gave **3h** (0.198 g, 67% yield) as a light yellow solid, R_f = 0.56 (40% ethyl acetate/hexanes), mp: 227−230 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (dd, J_1= 3.4 H_Z, J_2 = 5.7 H_Z, 1H), 7.62 (dd, J_1= 3.0 H_Z,

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J_2 = 6.2 H_Z, 1H), 7.44 (d, J = 3.3 H_Z, 1H), 7.43 (d, J = 3.1 H_Z, 1H), 7.35 (s, 1H), 6.99 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 158.4, 155.1, 152.9, 149.6, 146.7, 126.1, 125.0, 123.6, 121.5, 111.3, 104.5, 103.6, 101.7, 100.5, 56.3 × 2; IR ($CHCl_3$): 2917, 2849, 1722, 1515, 1459, 1444, 1270 cm^{-1}; HRMS (+ESI) Calcd for $C_{17}H_{13}O_5$ $[M + H]^+$: 297.0763; found: 297.0765.

*3,8,9-Trimethoxy-6H-benzofuro[3,2-c]chromen-6-one (**3i**).*[6a] Flash column chromatography on silica gel (35% ethyl acetate/hexanes) gave **3i** (0.212 g, 65% yield) as a light yellow solid, R_f = 0.48 (40% ethyl acetate/hexane); mp 230−233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J = 8.4 H_Z, 1H), 7.51 (s, 1H), 7.13 (s, 1H), 6.94−7.04 (m 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ162.4, 159.7, 158.8, 154.9, 149.9, 149.0, 147.9, 122.3, 115.5, 113.0, 106.3, 103.8, 102.2, 101.4, 95.5, 56.5, 56.4, 55.8; IR ($CHCl_3$): 2924, 2853, 1741, 1628, 1608, 1494, 1464, 1411, 1278, 1214, 1024, 837, 804, 765 cm^{-1}; HRMS (+ESI) Calcd for $C_{18}H_{15}O_6$ $[M + H]^+$: 327.0869; found: 327.0871.

*8,9-Dimethoxy-2,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (**3j**).* Flash column chromatography on silica gel (40% ethyl acetate/hexanes) gave **3j** (0.223g, 69% yield) as a brown solid, R_f = 0.52 (40% ethyl acetate/hexanes), mp 163 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.49 (s, 1H), 7.22 (s, 1H), 7.15 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 158.8, 151.5, 150.1, 149.2, 147.9, 141.2, 135.5, 121.2, 117.8, 115.5, 110.4, 105.1, 102.2, 95.5, 56.5, 56.3, 20.4, 19.4; IR ($CHCl_3$): 2925, 2854, 1733, 1631, 1595, 1511, 1419, 1351, 1272, 1213, 1023, 819, 803, 756, 664, 638, 584 cm^{-1}; HRMS (+ESI) Calcd for $C_{19}H_{17}O_5$ $[M + H]^+$: 325.1076; found: 325.1077.

*2-Methyl-6H-naphtho[2′,3′:4,5]furo[3,2-c]chromen-6-one (**3k**).* Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3k** (0.192 g, 64% yield) as a pale yellow sticky solid, R_f = 0.52 (10% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): 8.59 (s, 1H), 7.94−8.06 (m, 3H), 7.86 (s, 1H), 7.42−7.56 (m, 4H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 158.3, 153.9, 152.4, 135.7, 134.7, 133.7, 132.1, 128.5, 127.9, 126.2, 125.3, 123.4, 121.8, 120.4, 117.3, 112.1, 107.7, 105.2, 20.9 ; IR ($CHCl_3$): 2923, 2853, 1729, 1714, 1613, 1594, 1506, 1464, 1456, 1367, 1261, 1210, 805, 771, 666, 645 cm^{-1}; HRMS (+ESI) Calcd for $C_{20}H_{13}O_3$ $[M + H]^+$: 301.0865; found: 301.0867.

*3-Methoxy-6H-naphtho[2′,3′:4,5]furo[3,2-c]chromen-6-one (**3l**).* Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3l** (0.193 g, 61% yield) as a brown solid, R_f = 0.65 (20% ethyl acetate/hexanes); mp: 197−200 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.87−8.12 (m, 4H), 7.43−7.60 (m, 2H), 6.92−7.10 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 162.9, 158.2, 156.1, 153.8, 131.8, 131.4, 128.3, 127.9, 125.9, 125.2, 123.4, 123.2, 119.8, 113.2, 107.5, 105.6, 102.6, 101.4, 55.8 ; IR ($CHCl_3$): 3419, 2922, 2851, 1743, 1613, 1465, 1206, 1161, 1025, 937, 768, 746, 702 cm^{-1}; HRMS (+ESI) Calcd for $C_{20}H_{13}O_4$ $[M + H]^+$: 317.0814; found: 317.0819.

*2,3-Dimethoxy-6H-naphtho[2′,3′:4,5]furo[3,2-c]chromen-6-one (**3m**).* Flash column chromatography on silica gel (30% ethyl acetate/hexanes) gave **3m** (0.197 g, 57% yield) as a pale yellow sticky solid, R_f = 0.48 (in 40% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.94−8.05 (m, 3H), 7.50−7.55 (m, 2H), 7.39 (s, 1H), 7.00 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 158.5, 153.8, 153.6, 150.4, 146.9, 131.8, 131.5, 128.4, 127.9, 126.0, 125.3, 123.6, 119.9, 114.1, 107.5, 104.4, 102.0, 100.6, 56.5 × 2; IR ($CHCl_3$): 2960, 2925, 2854, 138, 1732, 1519, 1456, 1276, 1261, 1095, 1020, 800, 675, 664 cm^{-1}; HRMS (+ESI) Calcd for $C_{21}H_{15}O_5$ $[M + H]^+$: 347.0919; found: 347.0916.

*8-Methyl-6H-benzofuro[3,2-c]chromen-6-one (**3n**) and 9-Methyl-6H-benzofuro[3,2-c]chromen-6-one (**3o**) (~1:1 Mixture).*[6c] Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3n** and **3o** (0.195 g, 78% yield) as a yellow solid, R_f = 0.51 (in 10% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): 7.98 (m, 3H), 7.91 (s, 1H), 7.55−7.61 (m, 2H), 7.52 (d, J = 8.5 H_Z, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.39 (m, 2H), 7.26 (d, J = 8.0 H_Z, 2H), 2.52 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 159.4, 158.1, 158.0, 155.8, 153.8, 153.4, 153.3, 137.4, 135.0, 131.6, 131.5, 127.8, 126.4, 124.5, 124.4, 121.7, 121.6, 121.5, 121.1, 117.3, 117.2, 112.7, 112.6, 111.8, 111.1, 105.8, 105.5, 21.8, 21.2; IR ($CHCl_3$): 2921, 2853, 1742, 1631, 1598, 1450, 1410, 1260, 1094, 1080, 1029, 975, 811, 801, 752, 727, 666, 593 cm^{-1}; HRMS (+ESI) calcd for $C_{16}H_{11}O_3$ $[M + H]^+$: 251.0708; found: 251.0709.

*3-Methoxy-8-methyl-6H-benzofuro[3,2-c]chromen-6-one (**3p**) and 3-Methoxy-9-methyl-6H-benzofuro[3,2-c]chromen-6-one (**3q**) (~1:1.1 Mixture).* Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3p** and **3q** (0.207 g, 74% yield) as a pale yellow solid, R_f = 0.6 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.9 H_Z, 1H), 7.82−7.86 (m, 3H), 7.46 (d, J = 8.4 H_Z, 1H), 7.38 (s, 1H), 7.21(t, J = 8.5 H_Z, 2H), 6.90−6.97 (m, 4H), 3.88 (s, 6H), 2.50 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.8, 162.7, 160.7, 160.2, 158.5, 158.4, 155.6, 155.4, 155.3, 153.6, 136.7, 134.9, 127.2, 126.3, 123.5, 122.7, 122.6, 121.3, 120.9, 120.8, 113.0, 112.9, 111.7, 110.9, 105.9, 105.8, 103.3, 103.1, 101.3, 101.2, 55.7 × 2, 21.8, 21.3 cm^{-1}; IR ($CHCl_3$): 2925, 2854, 1733, 1632, 1511, 1493, 1418, 1350, 1272, 1213, 1101, 1056, 1022, 819, 803, 770, 666 cm^{-1}; HRMS (+ESI) Calcd for $C_{17}H_{13}O_4$ $[M + H]^+$: 281.0814; found: 281.0816.

*8-Methoxy-2,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (**3r**) and 9-Methoxy-2,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (**3s**) (~1:1.6).* Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3r** and **3s** (0.206 g, 70% yield) as a pale yellow solid, R_f = 0.6 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.6 H_Z, 1H), 7.72 (s, 1H), 7.70 (s, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.51(d, J = 9.0 Hz, 1H), 7.27 (s, 1H), 7.16 (d, J = 2.2 Hz, 1H), 6.99−7.07 (m, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H), 2.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 159.6, 159.3, 158.6, 158.5, 157.5, 156.5, 152.0, 151.7, 149.9, 141.9, 141.4, 133.5, 133.4, 128.5, 124.3, 121.7, 121.6, 121.2, 120.9, 117.9, 117.8, 115.4, 113.1, 112.1, 110.2, 110.1, 103.3, 96.7, 55.9, 55.7, 20.4, 20.3, 19.3 × 2 cm^{-1}(One peak is missing due to overlap); IR ($CHCl_3$): 2921, 2851, 1731, 1634, 1594, 1494, 1462, 1272, 1213, 1176 cm^{-1}; HRMS (+ESI) Calcd for $C_{18}H_{15}O_4$ $[M + H]^+$: 295.0970; found: 295.0972.

*3-Methoxy-6H-[1,3]dioxolo[4′,5′:5,6]benzofuro[3,2-c]chromen-6-one (Flemichapparin C; **3t**).*[6b,c] Flash column chromatography on silica gel (10% ethyl acetate/hexanes) gave **3t** (0.208 g, 67% yield) as a pale yellow solid, R_f = 0.52 (20% ethyl acetate/hexane); mp 271 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.85 (d, J = 8.1 Hz, 1H), 7.46 (s, 1H), 7.12 (s, 1H), 6.99−6.94 (m, 2H), 6.07 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 159.9, 158.4, 154.7, 150.5, 147.3, 146.0, 122.2, 116.9, 112.9, 106.1, 103.8, 101.8, 101.3, 100.1, 93.9, 55.7; IR ($CHCl_3$): 2953, 2919, 2851, 1742, 1633, 1471 cm^{-1}; HRMS (+ESI) Calcd for $C_{17}H_{11}O_6$ $[M + H]^+$: 311.0556; found: 311.0559.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01966.

Copies of ^{1}H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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